REMARKS/ARGUMENTS

Status of the Claims

Claims 1-6 are currently pending in this application.

Responses to the Rejections

Under 35 U.S.C. § 102(e)

Claims 1-3 and 6 are rejected under 35 U.S.C. §102(e) as being allegedly anticipated by McIntosh et al., U.S. Patent No. 6,685,936 ("the '936 patent"). Applicant respectfully traverses this rejection. To maintain a *prima facie* case of anticipation, the Examiner must demonstrate that each and every element as set forth in the claim is either expressly found or is inherently described in a single prior art reference. The identical invention must be shown in as complete detail as is contained in the ... claim. *see MPEP § 2131.* Applicant submits that the identical invention is not shown in the reference as is contained in the claim. Therefore, Applicant respectfully traverses this rejection.

The cells produced by the methods of the '936 patent are not identical to the cells of the instantly claimed invention. As the Examiner notes in the Office Action of October 10, 2006, the '936 patent "does not teach the same process of making the claimed suppressor T cells." *Office Action, p.2.* The processes described in the '936 patent result in a population of suppressor T cells which does not have identical characteristics to the cells of the instantly claimed invention.

As noted in the Horwitz declaration submitted in the response to office action filed August 21, 2006, the suppressor T cells of the '936 patent require the presence of CD8+ cells to maintain their suppressor activity. The CD4+ cells of the instantly claimed invention do not require the presence of CD8+ cells to have suppressive activity.

The Examiner asserts that the instant claims encompass a population of suppressor T cells generated by culturing enriched CD8+ T cells. Applicant respectfully disagrees. Although the claimed processes *can* induce CD8+ T cells to exhibit suppressor activity, (see claim 6), the presence of CD8+ T cells is not *required* for the suppressor activity exhibited by the claimed CD4+ cells. As disclosed in Example 1 of the application, CD4+ cells were isolated from the recipient and activated with TGF-β. CD8+ cells were not present in the system during the process of generating suppressor cells from these isolated CD4+ cells. Figures 2A through 4B show that the T cells generated using the disclosed process are able to block the ability of the recipient's T cells to kill donor cells.

In contrast, the '936 patent specifically discloses that the suppressive activity of its suppressor T cells requires CD8+ cells. *see Column 8, lines 19ff.* The '936 patent discloses that depletion of CD8+

cells resulted in only "partial suppression", and further makes the statement that the suppressor cells induced by the disclosed methods were CD8+ cells.

Furthermore, it is known in the art that the methods by which suppressor cells are induced can result in different types of cells, and the type of cells produced depends on the nature of the methods used. The '936 patent discloses preparation of suppressor cells by culturing activated T-cells with mesenchymal stem cells. The claimed suppressor T cells are produced by using a regulatory composition comprising TGF-β. Batten et al. (see Exhibit 1, enclosed herein) show that the cytokine profile of T cells after co-culture with mesenchymal stem cells is "distinctly different" than the cytokine profile of T cells after co-culture with peripheral blood mononuclear cells (PBMCs). A difference in cytokine profile means that suppressor cells produced with mesenchymal stem cells are not identical to suppressor cells produced using PBMCs.

Similarly, the claimed suppressor cells generated from recipient PBMC enriched for CD8+ T cells (see claim 6) are not identical to the CD8+ cells described in the '936 patent. CD8+ cells are known in the art to be CD28 negative (see Exhibits 2 and 3). However, as described in the accompanying declaration, CD8+ cells produced by the methods described in the present application are CD28 positive. Furthermore, regulatory compositions comprising TGF-β induce CD8+ suppressor cells which are both CD28 positive and also positive for the expression of the transcription factor Foxp3 (see Exhibit A of the accompanying declaration). Such CD8+CD28+Foxp3+ cells are rare in the blood and lymphoid organs of mice and humans. Thus, the suppressor cells generated from the claimed CD8+ cells are not identical to the CD8+ cells described in the '936 patent.

Since the cells disclosed in the '936 patent are not identical to the claimed cells, a rejection under §102 is improper, and Applicant respectfully requests that this rejection be withdrawn.

Under 35 U.S.C. § 102(b)

Claims 1-5 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Hall et al. ("Hall"). Applicant submits that the identical invention is not shown in the reference as set forth in the claims. Therefore, Applicant respectfully traverses this rejection.

The suppressor cells in Hall require the presence of CD8+ cells, which, as discussed above, is not true for the instantly claimed invention. The Examiner states that Hall teaches that CD8+ cells do not mediate suppression. *Office Action, p. 4, second paragraph.* Applicant respectfully disagrees. Table IV of Hall shows CD4+ suppressor cells can maintain tolerance to a foreign heart graft in adult animals that have been irradiated and thymectomized, and Hall speculates that the CD4+ cells may exert suppressive activity by themselves. However, in the data in Table V, Hall clearly shows that radioresistant CD8+ cells are required for the CD4+ suppressor cells to function, and on the next page, Hall explicitly states: "Taken together, these results show the rejection response in irradiated rats is inhibited by an MRC Ox8+

cell that was radioresistant but not thymus derived. This cell was critical for the transfer of suppression by the W3/25+ cells from CSA-treated hosts." *emphasis added, Hall, p.148, second full paragraph.* (Note that the MRC Ox8+ cells in Hall are CD8+ cells—see page 143 of Hall, first full paragraph). Hall clearly concludes that the CD4+ cells in its system require the presence of CD8+ cells to mediate suppressive activity.

The Examiner states that the MRC Ox8+ depletion experiments described in Hall suggest that CD4+ cells have suppressive activity on their own. However, this conclusion is incorrect, as shown by the above cited statement in Hall. Additionally, the reference enclosed herein as Exhibit 4 further shows that the methods disclosed in the instant application produce suppressor cells which act independently of CD8+ cells. There are no CD8+ cells in the experimental systems described in Exhibit 4, and yet the application of a regulatory composition comprising TGF-β induces CD4+ cells to have suppressor activity.

Furthermore, as discussed above, there is evidence in the literature that the method by which a suppressor cell is generated can affect the nature of that suppressor cell, and that different methods can produce different populations of suppressor cells. In the instantly claimed invention, a regulatory composition comprising TGF-β is used to induce suppressor T cells. Hall uses T cells from cyclosporine treated animals to produce suppressor T cells. It is known in the literature that TGF-β induces suppressor cells to express the transcription factor Foxp3, whereas cyclosporine in fact compromises the generation of cells expressing Foxp3. *compare Exhibit 5 to Exhibit 6.* The methods of Hall and the methods disclosed in the instant application produce two different populations of cells, and therefore Hall does not support an anticipation rejection. Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-442-1225.

A Petition for Three Months Extension of Time, with requisute fees, accompanies this Amendment. While no additional fee is believed to be due, if this belief is in error the Commissioner is authorized to charge any additional fees, including extension fees or other relief which may be required, or credit any overpayment to Deposit Account No. 50-0310 (Our Order No. 067797-5006-US01).

Respectfully submitted,

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Dated: April 10, 2007 By: /

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Enclosures:
Exhibit 1: Batten et al., *Tissue Eng.* 2006.
Exhibit 2: Zheng et al., *J. Immunol.* 2002.
Exhibit 3: Filaci et al., *Human Immunnol.* 2004.
Exhibit 4: Damle et al., *Clin. Immunol. Immunopath.* 1989.
Exhibit 5: Zhang et al., *J. Cell Physiol.* 2007.
Exhibit 6: Coenen, et al., *Bone Marrow Transplant.* 2007.